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Mildly abnormal general movement quality in infants is associated with higher Mead acid and lower arachidonic acid and shows a U-shaped relation with the DHA/AA ratio[☆]

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ABSTRACT

We showed that docosahexaenoic acid (DHA) supplementation during pregnancy and lactation was associated with more mildly abnormal (MA) general movements (GMs) in the infants. Since this finding was unexpected and inter-individual DHA intakes are highly variable, we explored the relationship between GM quality and erythrocyte DHA, arachidonic acid (AA), DHA/AA and Mead acid in 57 infants of this trial. MA GMs were inversely related to AA, associated with Mead acid, and associated with DHA/AA in a U-shaped manner. These relationships may indicate dependence of newborn AA status on synthesis from linoleic acid. This becomes restricted during the intrauterine period by abundant *de novo* synthesis of oleic and Mead acids from glucose, consistent with reduced insulin sensitivity during the third trimester. The descending part of the U-shaped relation between MA GMs and DHA/AA probably indicates DHA shortage next to AA shortage. The ascending part may reflect a different developmental trajectory that is not necessarily unfavorable.

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1. Introduction

The long chain polyunsaturated fatty acids (LCP) arachidonic acid (AA; 20:4n–6), eicosapentaenoic acid (EPA; 20:5n–3) and docosahexaenoic acid (DHA; 22:6n–3) are structural components of membrane phospholipids, modulators of gene expression and precursors of eicosanoids (AA, EPA), resolvins (AA, EPA and DHA) and (neuro)protectins (DHA) [1,2]. EPA and DHA are mainly derived from fish, while meat, poultry and eggs are the main sources of dietary AA. Both AA and DHA are considered important for brain development.

We recently reported results of supplementing healthy pregnant women with DHA+AA (220 mg each/day), DHA (220 mg/day) or placebo from week 17 of pregnancy till 12 weeks after term delivery. The primary endpoint was the infants general movement (GM) quality [3]. GMs are movements involving all body parts, they are characterized by variation, complexity and fluency [4]. They emerge during early fetal life and disappear at about 4 months post-term when goal-directed movements

emerge. The typical characteristics of GMs disappear in case of dysfunction [5]. General movements can be qualified as normal optimal (NO), normal suboptimal (NS), mildly abnormal (MA) or as definitely abnormal (DA), of which the latter is considered to be of clinical relevance [5]. Our study revealed that infants in the DHA group showed more MA GMs as compared to the placebo group and the DHA+AA group, whereas the placebo and DHA+AA groups did not differ in GM quality.

The finding that DHA supplementation resulted in more MA GMs was unexpected, since generally DHA status is positively associated with neurological development, although reviews and meta analyses [6–8] of DHA supplementation studies show no effect or are at best inconclusive. We hypothesized that GM quality is sensitive to the DHA/AA balance. Alternatively, the relation between maternal DHA intake and parameters for neurological development of their offspring may be non-linear, for which there is some evidence from studies in rats [9] and humans [10]. Moreover, fish consumption is subject to high inter-individual variation and consequently, at the study end, subjects with low background intakes in the intervention group may have a DHA status similar to, or even lower than, that of subjects with high background DHA intakes residing in the placebo group.

In view of the unexpectedness of the outcome of our trial and the highly variable inter-individual DHA status, we studied the relation between the LCP status at the study end and neurological

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development. For this, we investigated the relationships of the infant's GM quality at 12 weeks of age with the infant's red blood cell (RBC) DHA, AA and Mead acid (20:3n–9; parameter of EFA/LCP deficiency) contents, as well as the RBC DHA/AA ratio.

2. Subjects and methods

The study design has been reported in detail elsewhere [3]. Briefly, healthy women during their first or second pregnancy, were enrolled around week 17 of pregnancy (mean: 16.5 weeks postmenstrual age). Exclusion and termination criteria were a vegan diet, (gestational) diabetes mellitus and preterm birth (before 37 weeks of pregnancy). At enrolment, women were randomized to three groups. All participants received a vitamin and mineral supplement containing the Dutch recommended dietary allowance for pregnant women. In addition, the women received placebo (soy bean oil), DHA (220 mg/day) or DHA+AA (220 mg each/day). The research protocol was approved by the Central Committee on Research Involving Human Subjects (CCMO, Den Haag, The Netherlands; protocol number P03.1071C). All women gave written informed consent. The trial is registered under ISRCTN58176213.

2.1. Neurological examination

The infant's neurological condition was assessed by establishing the GM quality in the 12th postnatal week. To this end, spontaneous motility in supine position was videotaped for at least 5 min. Movements were recorded while the infant was awake, active and not crying. GM quality was assessed according to Hadders-Algra et al. [11], i.e. movements were classified as normal optimal (NO), normal suboptimal (NS), mildly abnormal (MA) or definitely abnormal (DA).

2.2. Characteristics

We used the Obstetrical Optimality Score (OOS) form to obtain data on socioeconomic status, non-obstetrical conditions during pregnancy, obstetrical past history, diagnostic and therapeutic measures, parturition and neonatal condition immediately after birth [12].

2.3. Sample collection and fatty acid analyses

EDTA-anticoagulated blood from the infants was collected 12 weeks after birth, for the isolation of RBC (throughout referred to as infant RBC; iRBC) After washing the RBC three times with 0.9% saline, 200 μ L of a 50% hematocrit suspension was transferred into a Sovirel tube. The Sovirel tubes contained 2 mL methanol/HCl (5:1, v/v), 5 mg butylated hydroxytoluene (antioxidant) and 50 μ g 17:0 (internal quantification standard). Following transmethylation, fatty acid compositions were determined by using our previously described capillary gas chromatographic method with flame-ionization detection [13]. Fatty acid compositions were calculated assuming that equal peak areas give rise to equal weight amounts [14]. Fatty acids are presented in wt% or wt/wt. We focused on DHA, AA, Mead acid and the DHA/AA ratio.

2.4. Statistical analyses

Statistics were performed using the software package SPSS, version 16. Univariate differences for perinatal and social characteristics were evaluated by using either a chi-square test (for categorical variables) or a *t*-test (for continuous variables). For DHA, AA, DHA/AA and Mead acid, we created univariate logistic

regression models. To test whether there were non-linear relations between fatty acids and GM-quality, we added a quadratic term to the model to test for U-shape or bell-shape. In case changes in GM-quality seemed to reach a plateau at a certain wt%, we dichotomized the continuous variable at the plateau level. We also created a multivariate logistic regression model with GM quality as dependent variable and the fatty acids as well as relevant perinatal and social characteristics as covariates to study which variables are most predictive for GM quality. $p < 0.05$ was considered significant.

3. Results

A total of 183 pregnant women were included. Of these, GM quality and perinatal data were available from 119 mother–infant pairs. Blood samples were collected from 57 infants. Reasons for drop-out were lack of motivation to take supplements daily and to fill in questionnaires on a regular basis (58 cases), preterm delivery (4 cases), other pregnancy complications (2 cases) and no parental permission for infant blood sampling (62 cases). There were no differences in GM quality and prenatal, perinatal or social characteristics between the infants of whom blood was collected compared to those of whom blood was not available (data not shown). All cases of drop-out were evenly distributed among the three treatment groups.

Table 1 shows prenatal, perinatal and social characteristics of the 57 mother–infant pairs who were included in this study. For statistical purposes, we recoded NO and NS GMs into normal (N) GMs. None of the infants showed DA GMs. Thirty infants were classified as having normal GMs (3 NO and 27 NS GMs) and 27 had MA GMs. Mothers of infants with MA GMs were younger and had a lower educational level ($p < 0.05$), they did not differ in parity. Infants with N GMs did not differ in gender, birth weight and gestational age at birth from infants with MA GMs. Frequency of exclusive breastfeeding was similar in the two groups.

Fig. 1 shows the percentages MA GMs as functions of iRBC DHA (panel A), AA (panel B), DHA/AA ratio (panel C) and Mead acid (panel D). The iRBC data were clustered into sixtiles for visual evaluation. Univariate analysis revealed that there was no significant relation between GM quality and DHA status. A higher iRBC AA was associated with less MA GMs (Nagelkerke r^2 0.12; model χ^2 5.39; model $p=0.020$). The iRBC DHA/AA ratio was related to the occurrence of MA GMs in a U-shaped manner, i.e. both low and high iRBC DHA/AA ratios were associated with high rates of MA GMs (Nagelkerke r^2 0.20; model χ^2 9.03; model $p=0.011$). The lowest percentage MA GMs (about 25%) was observed at iRBC DHA/AA ratios ranging from 0.32–0.36 (wt/wt). An increasing iRBC Mead acid was associated with an increasing rate of MA GMs, a 60–70% MA GMs plateau was reached at an iRBC Mead acid of about 0.40 wt% (Nagelkerke r^2 0.24; model χ^2 11.25; model $p=0.001$).

Table 1

Prenatal, perinatal and social characteristics of the 57 mother–infants pairs included in the study.

	N GMs (n=30)	MA GMs (n=27)
Maternal age (y) (mean \pm sd)	32.7 \pm 4.4	29.4 \pm 3.6*
Maternal higher education ^a [n(%)]	28 (93)	18 (67)*
First born [n(%)]	17 (57)	13 (48)
Gestational age at birth (wk) (mean \pm sd)	40.5 \pm 0.9	40.0 \pm 1.4
Gender male [n(%)]	17 (57)	10 (37)
Birth weight (g) (mean \pm sd)	3689 \pm 440	3463 \pm 471
Exclusively breastfed infants ^b [n(%)]	18 (60)	18 (67)

N GMs, normal general movements; MA GMs, mildly abnormal general movements; *different from normal GMs at $p < 0.05$; ^ahigh school completed; ^bat time of examination (12 postnatal weeks).

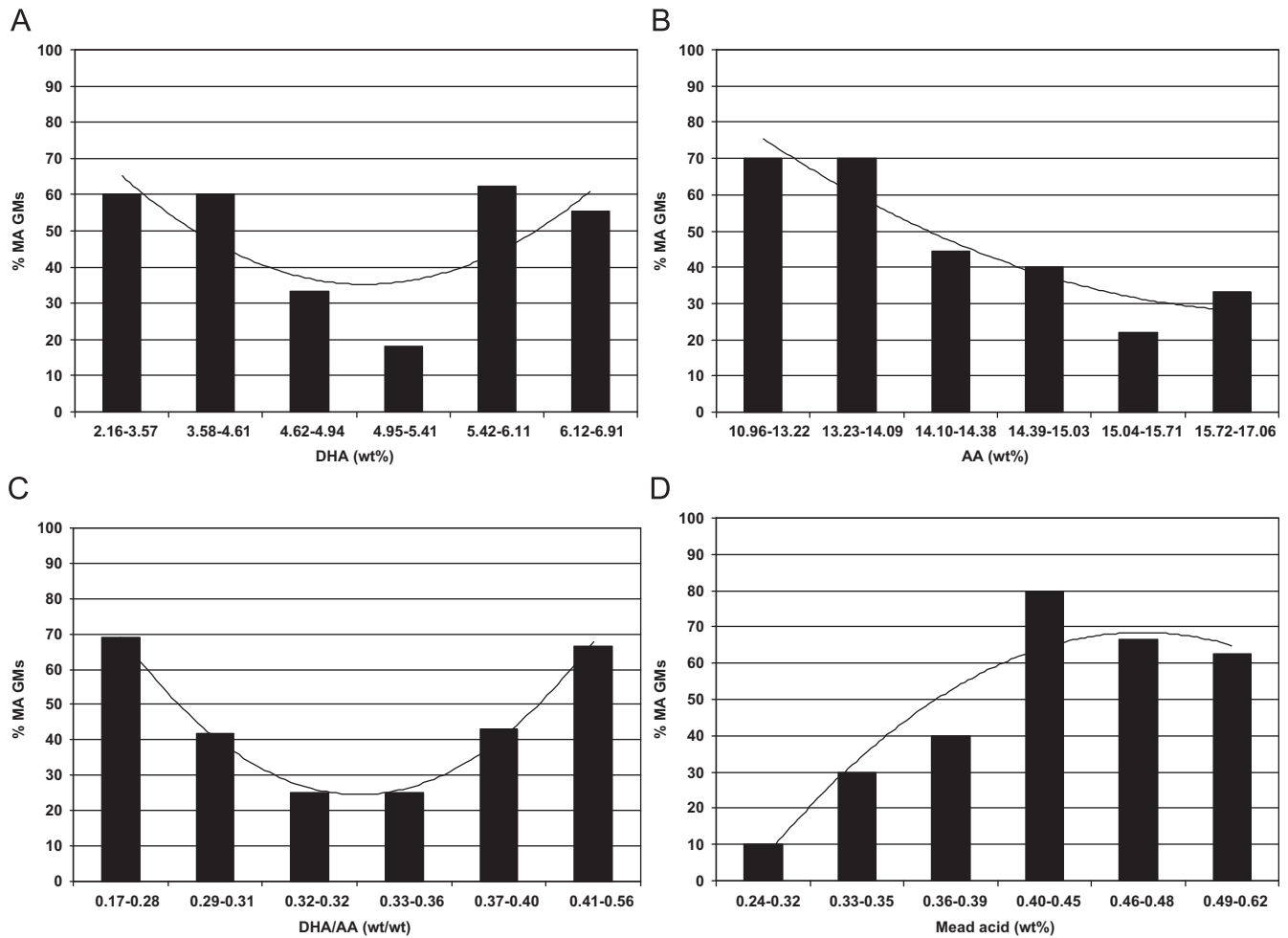


Fig. 1. Percentage infants with mildly abnormal GMs as a function of iRBC DHA, AA, DHA/AA and Mead acid. MA GMs, mildly abnormal general movements. There is no significant relation between DHA and GM quality. MA GMs are inversely related to AA, are associated with Mead acid, and are associated with DHA/AA in a U-shaped manner. The U-shaped curve does not imply an optimum at 0.32–0.33 DHA/AA, but might indicate a different developmental trajectory at the ascending part of the curve, which is not necessarily unfavorable.

Table 2

Logistic regression analyses of factors contributing to the rate of mildly abnormal GMs in the 12th postnatal week.

	Exp B (95% CI)	p
iRBC Mead acid (g%) ^a	11.80 (2.57–54.21)	0.002
Maternal age at baseline (y)	0.78 (0.64–0.95)	0.013
Maternal education ^b	0.11 (0.01–0.89)	0.039
Constant	4154.46	0.011

Factors were considered to be significant at $p < 0.05$. Explained variance of the model 49.1% (Nagelkerke), model χ^2 , 26.1; $p < 0.001$. ^aDichotomized at 0.40 g%; 0 < 0.40 g%, 1 \geq 0.40 g%; ^b0=lower education, 1=higher education, i.e. high school completed. CI, confidence interval; iRBC, infant red blood cell at 12 weeks of age.

Table 2 shows the final results of multivariate logistic regression analyses. iRBC Mead acid values above 0.40 wt% were associated with increased odds of MA GMs, whereas both higher maternal age and higher maternal education were associated with decreased odds of MA GMs.

4. Discussion

We studied the relations between the iRBC DHA, AA and Mead acid contents, and the iRBC DHA/AA ratio on the one hand and GM

quality at 3 months of age on the other hand. The percentage MA GMs proved: (1) inversely related to iRBC AA, (2) associated with iRBC Mead acid according to a saturation curve and (3) associated to the iRBC DHA/AA ratio in a U-shaped manner. In multivariate logistic regression, iRBC Mead acid proved strongest related to GM quality and to a lesser extent with maternal age and maternal education. The strength of the study is the employment of a sensitive method for the assessment of neurodevelopment, while it is limited by the relatively small number of infants, which, however, did not hamper the observational power of the study.

The relation between GM quality and AA status is in accordance with a previous study from our group [15], in which GM quality also proved positively associated with AA and negatively with total n-9 fatty acids and oleic acid (OA, 18:1n-9) contents and the Mead acid/AA ratio of umbilical arteries. The different directions of the relations of GM quality with AA and n-9 fatty acids are conceivable, since there are strong metabolic relations between AA and OA, and between AA and Mead acid in umbilical vessel walls [16]. In addition, Helland et al. found a relation between umbilical plasma Mead acid and intelligence scores at 4 years of age [17].

High iRBC Mead acid in the postnatal period is conceivably a remnant of intrauterine conditions, since the initially high levels at birth gradually disappear with advancing postnatal age [18]. The abundant intrauterine synthesis of Mead acid [19] is a

consequence of the high *de novo* synthesis of OA from the ample glucose that crosses the placenta in the third trimester [20]. Together with other *de novo* synthesized fatty acids, OA constitutes about 80% of the fatty acids that accumulate in the newborn's fat mass [21]. The fetus synthesizes abundant OA, but receives limited fatty acids across the placenta [22] and is inefficient in trapping free linoleic acid (LA, 18:2n-6) as shown at least in primates [23]. This contributes to a high fetal OA/LA ratio that stimulates fetal delta-6 desaturase (FADS2) to synthesize Mead acid from OA, at the expense of AA from LA. Consistent with this notion are the observations that Mead acid in umbilical vessel walls exhibits a positive relation with OA, and negative correlations with both AA and LA [16]. In addition there is competition between Mead acid and AA for incorporation into tissue lipids, since it was shown in rats that supplementation with Mead acid causes displacement of AA, notably at low LA intakes [24]. In other words, it seems that both fetal and early postnatal Mead acid indicate intrauterine restricted AA synthesis and incorporation.

Mead acid synthesis may become amplified by excessively high fetal *de novo* fatty acid synthesis from glucose in the third trimester due to abnormally low maternal insulin sensitivity. This causes even more successful competition of *de novo* synthesized OA for delta-6 desaturase and the occurrence of a state of 'relative EFA/LCP deficiency', rather than an absolute deficiency [25]. Such conditions have been encountered in maternal diabetes mellitus type 2, gestational diabetes [25,26] and preeclampsia [27], which may carry a common denominator in maternal insulin resistance. The underlying mechanisms might be higher transplacental glucose flux with concomitantly increased fetal *de novo* fatty acid synthesis in (gestational) diabetes, and highly increased *de novo* fatty acid synthesis in the maternal liver [28] with subsequent presentation of these fatty acids for transplacental transfer in (gestational) diabetes and preeclampsia.

Abundant fetal Mead acid synthesis is unlikely to be a consequence of insufficient AA status and high *de novo* fatty acid synthesis only. It also requires low DHA, since both AA and DHA are known to cause feedback inhibition of delta-6 desaturase [29]. The origin of low fetal DHA is low maternal DHA, since DHA is preferentially transported across the placenta, compared with AA, ALA and LA [30]. The currently employed relatively low maternal supplemental DHA dose (i.e. 220 mg/day), the insufficient DHA background intake by Dutch women (about 84 mg LCPn-3/day in 2003 [31]; Dutch recommendation 450 mg LCPn-3/day), the decreasing LCPn-3 intake during the last decades in Western countries in general [32], and depletion of maternal AA and notably DHA during pregnancy and subsequent lactation [33] are likely to result in marginal fetal DHA status. Although not defined for infants, none of the infants in our study complied with the > 8 wt% RBC EPA+DHA as set by Von Schacky and Harris [34], which criterion confers 90% less risk for sudden cardiac death in adults, as compared to an omega-3 index of < 4%. In addition, only two of the DHA-supplemented mothers met this recommendation (data not shown).

The relation of GM quality with DHA (Fig. 1, panels A and C) proved different from the relation with AA. Generally, brain DHA is more sensitive to dietary DHA than brain AA is to dietary AA, which has been shown in baboons [35] and may also be derived from autopsy studies in breast and formula fed infants [36–38]. The descending part of the U-shaped relation between GM quality and the iRBC DHA/AA ratio (Fig. 1, panel C) may indicate a similar adverse effect of low fetal DHA status as described above for AA. Moreover, with decreasing DHA/AA ratio, or with decreasing DHA status, brain development will become compromised, as notably shown in animal studies [6]. It has been established that low brain DHA/AA ratio is related to (neuro)inflammation [39].

The ascending part of the U-shaped iRBC DHA/AA curve (Fig. 1, panel C) is, however, likely to have a different explanation. It is well known that the various parts of the fetal brain have different DHA and AA contents and that not all parts are equally sensitive to dietary DHA alterations. For instance, Hsieh et al. [35] showed that the newborn baboon cerebral cortex DHA content still increases at higher DHA intakes, while basal ganglia and limbic system DHA already saturate at lower intakes. The ascending part of the U-shaped curve, although indicating an increase of MA GM quality with increasing DHA/AA ratio, does not exclude a beneficial effect of DHA for some parts of the brain and their functions at later age, or may indicate a different developmental trajectory. The beneficial effects of a higher than current DHA status is increasingly acknowledged, as may e.g. be derived from the recent adjustment of the recommended daily intake of LCPn-3 from 200 to 450 mg, while there is a good evidence that even higher intakes may be needed, at least for prevention of coronary heart disease [40].

Interestingly, U- or bell-shaped curves similar to ours were shown by Levant et al. [9] and Jacobson et al. [10]. Levant et al. [9] showed that variation in rat brain DHA content by dietary means caused sex-specific alterations in locomotor activity, with males being most affected notably at post-adolescent age. The observed DHA intake-effect curve proved bell-shaped, with both low and high DHA intakes giving rise to lower locomotor activities compared with control and medium low DHA intakes. Although un-commented by the authors, Jacobson et al. [10] showed a U-shaped relation between cord plasma phospholipid DHA and the Bayley Scales Psychomotor Development Index (PDI) at 11 months in breastfed Inuit infants with high DHA intakes living in the Arctic region. In addition, Church et al. [41] showed that excess as well as deficient n-3 fatty acid intakes during pregnancy and lactation cause impaired neural transmission in rats [41]. In human infants, negative associations between higher DHA intakes and verbal skills have been reported [42,43].

What brain areas are involved in the ascending part of the curve might become suggested from studies in newborn baboons. These show that the brain motor areas are not only highest in DHA (and AA) contents [44], but also the most sensitive to DHA supplementation [35]. Experiments with young rats revealed that fish oil supplementation influences several neurochemical and behavioral features of monoaminergic function, causing an increase of cerebral membrane phosphatidylserine, higher dopamine, reduction of monoamineoxidase-B activity and greater binding to dopamine D2 receptors in the frontal cortex, and also lower ambulatory activity [45]. Taken together, these data suggest that the U-shaped dose-response curves of the locomotion parameters of Levant et al. [9], the PDI of Jacobson et al. [10] and general movements (this study) have a common denominator in the modulation of the developing motor areas by dietary DHA.

U-shaped dose-response curves are not uncommon [46]. Of these, the effect of alcohol on coronary artery disease [47] is probably best known, while also micronutrient dose-response curves are classical examples [48]. The pathophysiological effects in U-shaped curves in the descending (i.e. deficient) and ascending (i.e. toxicological) parts usually reflect different underlying mechanisms leading to the common denominator of 'unfavorable effects'. Consequently, it is possible that the descending and ascending parts of the iRBC DHA/AA dose-response curve indicate different neurodevelopmental trajectories that nevertheless are preceded by similar MA GMs. Within the current iRBC DHA/AA range, these seemingly opposing developmental trajectories are unlikely to cause different neurodevelopmental outcomes at later age, as suggested by the negative outcomes of meta analyses of LCP supplementation studies [6,8]. It is possible that within the currently investigated

DHA/AA ratio they simply reflect the remarkable plasticity of brain development.

5. Conclusions

The assessment of GM quality proved a highly sensitive tool for studying the influence of LCP on neurodevelopment, since no test for neurodevelopment, apart from those assessing visual acuity, has as yet proven to be comparably sensitive to changes in LCP status. MA GM quality exhibits an inverse relationship with AA status and a saturating positive relationship with Mead acid. These relationships may indicate the dependence of newborn AA status on synthesis from LA, which conversion becomes restricted during the intrauterine period by *de novo* synthesis of OA and Mead acid from glucose, consistent with the reduced maternal insulin sensitivity of the third trimester. MA GM quality also exhibits an inverse relation with the DHA/AA ratio, which probably indicates DHA shortage next to AA shortage. However, the latter relationship shows a nadir, after which the relation becomes positive. We speculate that this ascending part of the U-shaped dose-response curve reflects a different developmental trajectory that might be related to motor areas and is not necessarily unfavorable.

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